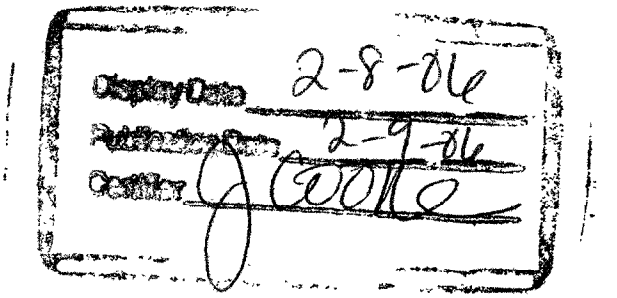
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866



[Docket No. 2003P–0564]

Microbiology Devices; Reclassification of Hepatitis A Virus Serological Assays

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to reclassify hepatitis A virus (HAV) serological assays from class III (premarket approval) into class II (special controls). FDA is taking this action after reviewing a reclassification petition submitted by Beckman Coulter, Inc. Elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of the guidance document entitled "Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Hepatitis A Virus Serological Assays" that will serve as the class II special control for these devices.

DATES: This rule is effective [*insert date 30 days after date of publication in the* **Federal Register**].

FOR FURTHER INFORMATION CONTACT: Sally Hojvat, Center for Devices and Radiological Health (HFZ–440), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 240–276–0496.

SUPPLEMENTARY INFORMATION:

I. Background

The Federal Food, Drug, and Cosmetic Act (the act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Public Law 94–295), the Safe Medical Devices Act (SMDA) (Public Law 101–629), and the Food and Drug Administration Modernization Act (FDAMA) (Public Law 105–115), established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513 of the act, devices that were in commercial distribution before May 28, 1976 (the date of enactment of the 1976 amendments), generally referred to as preamendments devices, are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976, generally referred to as postamendments devices, are classified automatically by statute (section 513(f) of the act) into class III without any FDA rulemaking process. Those devices generally remain in class III until the device is reclassified into class I or II, or FDA issues an order finding the device to be substantially equivalent, under section 513(i) of the act, to a legally marketed device. The agency determines whether new devices are substantially

equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the act (21 U.S.C. 360(k)) and 21 CFR part 807.

A preamendments device that has been classified into class III may be marketed, by means of premarket notification procedures, without submission of a premarket approval application (PMA) until FDA issues a final regulation under section 515(b) of the act (21 U.S.C. 360e(b)) requiring premarket approval.

Section 513(f)(3) allows FDA to initiate reclassification of a postamendments device classified into class III under section 513(f)(1) of the act, or the manufacturer or importer of a device to petition the Secretary of the Department of Health and Human Services for the issuance of an order classifying the device into class I or class II. FDA's regulations in section 21 CFR 860.134 set forth the procedures for the filing and review of a petition for reclassification of such class III devices. To change the classification of the device, it is necessary that the proposed new classification have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use.

II. Regulatory History of the Device

In the **Federal Register** of September 30, 2004 (69 FR 58371), FDA published a proposed rule to reclassify HAV serological assays into class II, after reviewing information contained in a reclassification petition submitted by Beckman Coulter, Inc. HAV serological assays are in vitro diagnostic devices used to support the clinical laboratory diagnosis of HAV. Specimens from individuals who have symptoms consistent with acute HAV or who may have previously been infected with HAV are tested for HAV-specific antibodies. The presence of these HAV-specific antibodies in human serum or plasma is

laboratory evidence of HAV infection. Interested persons were invited to comment on the proposed rule by December 29, 2004. FDA also identified the draft guidance document entitled "Class II Special Controls Guidance Document: Hepatitis A Serological Assays for the Clinical Laboratory Diagnosis of Hepatitis A Virus" as the proposed special control capable of providing reasonable assurance of safety and effectiveness for these devices.

III. Analysis of Comments and FDA's Response

FDA received several comments on the proposed rule and guidance document. One comment supported the reclassification of HAV serological assays stating that these devices afford a long history of safe and effective use and that class II status would be appropriate. Another comment supported the proposed reclassification of HAV serological assays, but suggested modified wording to clarify the definition of "human tissue" as used in the codification language and in the guidance document. FDA believes the use of "solid or soft tissue donors" adequately describes the individuals who are currently required to be tested.

Other comments suggested specific modifications to the documents. One suggestion was to broaden the scope to include the intended use of determining whether individuals are susceptible to HAV infection. FDA agreed with the suggestion and revised language in the guidance document and classification regulation. These comments also suggested revising the general study recommendations in the following ways:

(Comment 1) One comment recommended that the study include a representative sample of vaccines currently licensed in the United States, rather than every vaccine that is currently licensed in the United States. FDA disagrees with this comment. FDA believes it is essential to have data to show

that the submitted assay will detect antibodies produced from any U.S.-licensed vaccine.

(Comment 2) A comment recommended removing or revising the recommendation that manufacturers collect samples beginning at 2 to 4 weeks. FDA has clarified this section to recommend collecting specimens no earlier than 4 weeks post-vaccination.

(Comment 3) Another comment recommended FDA remove or revise the recommendation that a manufacturer establish reproducibility for devices indicated for use in matrices other than serum. FDA concurs and has revised this recommendation and added information within the guidance document to address this issue.

(Comment 4) Another comment asked FDA to remove the notation of anti-nuclear antibodies, rheumatoid factor, and heterophilic antibodies under the "interference" section because it is duplicative of the analysis recommended under the "cross-reactivity" section. FDA concurs and has revised the guidance document accordingly.

(Comment 5) Another comment asked FDA to clarify the recommended study population. FDA has revised the appropriate section of the guidance document to clarify the recommended study population, taking into account the sporadic incidence of HAV infection within the United States.

IV. Conclusion

Based on the information discussed in the preamble to the proposed rule (69 FR 58371), FDA concludes that special controls, in conjunction with general controls, will provide reasonable assurance of the safety and effectiveness for HAV serological assays. The agency is, therefore, reclassifying HAV serological assays from class III (premarket approval) into class II (special controls). Elsewhere in this issue of the **Federal Register**, FDA is announcing

the availability of the guidance document entitled "Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Hepatitis A Virus Serological Assays" as the special control capable of providing reasonable assurance of safety and effectiveness for these devices. Following the effective date of this final classification rule, any firm submitting a 510(k) premarket notification for a HAV serological assay will need to address the issues covered in the special controls guidance. However, the firm need only show that its device meets the recommendations of the guidance or in some other way provides equivalent assurances of safety and effectiveness.

FDA is now codifying the classification for HAV serological assays by adding new § 866.3310. For the convenience of the reader, 21 CFR 866.1 informs the reader where to find guidance documents referenced in 21 CFR part 866.

Section 510(m) of the act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. For this type of device, FDA has determined that premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device and, therefore, this type of device is not exempt from premarket notification requirements. Persons who intend to market this type of device must submit to FDA a premarket notification, prior to marketing the device, which contains information about the HAV serological assay they intend to market.

V. Environmental Impact

The agency has determined under 21 CFR 25.34(b) that this reclassification action is of a type that does not individually or cumulatively have a significant

effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is not a significant regulatory action under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Reclassification of HAV serological assays from class III into class II will relieve manufacturers of the cost of complying with the premarket approval requirements in section 515 of the act. Because reclassification will reduce regulatory costs with respect to these devices, it will impose no significant economic impact on any small entities, and it may permit small potential competitors to enter the marketplace by lowering their costs.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after

adjustment for inflation is $115 million, using the most current (2003) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required

VIII. Paperwork Reduction Act of 1995

FDA concludes that this rule contains no new collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

List of Subjects in 21 CFR Part 866

Biologics, Laboratories, Medical devices.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 866 is amended as follows:

PART 866—IMMUNOLOGY AND MICROBIOLOGY DEVICES

■ 1. The authority citation for 21 CFR part 866 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

■ 2. Section 866.3310 is added to subpart D to read as follows:

§ 866.3310 Hepatitis A virus (HAV) serological assays.

(a) *Identification.* HAV serological assays are devices that consist of antigens and antisera for the detection of hepatitis A virus-specific IgM, IgG, or total antibodies (IgM and IgG), in human serum or plasma. These devices are used for testing specimens from individuals who have signs and symptoms consistent with acute hepatitis to determine if an individual has been previously infected with HAV, or as an aid to identify HAV-susceptible individuals. The detection of these antibodies aids in the clinical laboratory diagnosis of an acute or past infection by HAV in conjunction with other clinical laboratory findings. These devices are not intended for screening blood or solid or soft tissue donors.

(b) *Classification.* Class II (special controls). The special control is "Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Hepatitis A Virus Serological Assays." See § 866.1(e) for the availability of this guidance document.

Dated: 2/1/06

February 1, 2006.

Linda S. Kahan

Linda S. Kahan,
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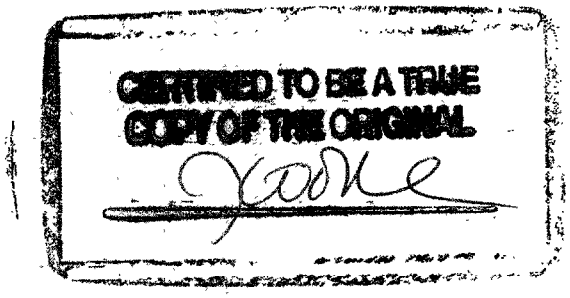
Center for Devices and Radiological Health.



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